REMARKS

Claims 5, 7-9, 26, 27, 29, 31, 37, 48-51, 56, 58, 69, 70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, 156, and 157 are pending in the present application. Claims 56, 110, 135, 137, 147, and 150 remain withdrawn from consideration as directed to a non-elected invention or species.

Applicants have amended independent claim 5 to clarify structural features of the targeting domain. Applicants' amendment is fully supported by the specification and claims, prior to Amendment.

Applicants have amended claim 69 to clarify that the adzyme is resistant to *autocatalysis* by the protease domain. Support for Applicants' amendment can be found throughout the specification. Exemplary support can be found in paragraphs [0012], [0021], [0031], [0041], [0069], and [0407]-[0417] of the published specification.

Applicants have also amended claim 74 to clarify that the adzyme *inhibits* a biological activity of said substrate. Support for Applicants' amendment can be found throughout the specification. Exemplary support can be found in paragraphs [0067], [0068], [0121], [0176], and [0202] of the published specification.

Applicants hereby add new claims 158-163. Support for the subject matter of the newly added claims is found throughout the specification and previously pending claims. Specifically, new claim 158 is completely within the scope of claims 48 and 49, prior to the instant Amendment. Accordingly, no new matter has been entered. Moreover, Applicants submit that claims 158-163 are completely within the scope of the subject matter already searched and considered by the Examiner.

Applicants' amendments and new claims are fully supported by the specification and do not add new matter. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim Rejection - 35 U.S.C. § 112, second paragraph

Claims 69 and 74 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that

Applicants regard as the invention. The Examiner asserts that the recitation of the term "resistant to cleavage by the protease domain" in claim 69 renders the claim indefinite because the resulting claim does not set forth the metes and bounds of the desired patent protection. The Examiner further asserts that the recitation of the term "reduces a biological activity" makes claim 74 unclear because "reduces a biological activity" is a relative term. Applicants respectfully traverse the rejection.

In claim 69, the term "resistant to cleavage by the protease domain" is supported in the section of the specification entitled "Resistance to Autocatalysis" (paragraphs [0407] to [0417]). In view of the detailed teachings provided in the specification, one of skill in the art can readily appreciate the metes and bounds of the claims. Applicants note that the standard for evaluating compliance with § 112, second paragraph, "is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." MPEP 2173.02. In fact, the Office directs Examiners to "allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." *Id.* (Emphasis in the original).

This same portion of the MPEP provides detailed guidance for evaluating definiteness of claim language and specifically cautions against analyzing such language in a vacuum. Rather, claim language must always be analyzed in view of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Moreover, Applicants note that the Federal Circuit uses a high threshold for concluding that a claim is indefinite. "The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles ... Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, (Fed. Cir. 2004).

In view of the standards and guidance set forth in MPEP 2173.02 and articulated by the Federal Circuit, Applicants contend that claim 69 defines the metes and bounds of the claimed

subject matter with particularity. Nevertheless, to expedite prosecution, Applicants have amended claim 69 to specify that the adzyme is resistant to *autocatalysis*. In view of Applicants' amendment, claim 69 more closely mirrors the detailed description provided, for example, in paragraphs [0407] to [0417] of the published specification. Applicants' amendment is made solely for clarity and is not believed to alter the scope of the claims.

Applicants' amendment is made solely to expedite prosecution and is not in acquiescence to the rejection. Applicants expressly reserve the right to prosecute claims using the same or differing language, including claims of similar or differing scope, in future applications.

In claim 74, the basis of the Examiner's rejection appears to be the use of relative terminology for describing the claimed invention. However, in accordance with MPEP 2173.05, the use of relative terminology "does not automatically render the claim indefinite." Rather, the standard when assessing relative terminology is "whether one of ordinary skill in the art would understand what is claimed, in light of the specification." *Id.* Thus, the standard for assessing relative terminology is no different than that for assessing compliance with § 112, second paragraph, more generally, as detailed in MPEP 2173.02 and outlined above.

Applicants contend that the metes and bounds of claim 74 are clear. Applicants note that the Examiner himself was able to construe the claim, as set forth in the construction provided on page 2 of the instant Office Action. This further supports Applicants' position that claim 74 is clear, and that one of skill in the art would readily appreciate that the reduction in biological activity is a reduction relative to that observed in the absence of treatment with the adzyme.

Nevertheless, to expedite prosecution, Applicants have amended claim 74 to incorporate the Examiner's suggestion which explicitly states what would be well understood by one of skill in the art. Specifically claim 74 has been amended to point out that the biological activity is assessed *relative to said biological activity in the absence of said adzyme*. Additionally, Applicants have amended claim 74 to replace the term "reduces" with "inhibits", thereby providing consistency with the discussion provided in numerous places throughout the specification. *See*, for example, paragraphs [0067], [0068], [0121], [0176], and [0202] of the published specification.

Applicants' amendment to claim 74 is solely to expedite prosecution and is not in acquiescence to the rejection. Applicants expressly reserve the right to prosecute claims using

similar or differing language, including claims of similar or differing scope.

In view of the foregoing arguments, Applicants submit that claims 69 and 74 are fully compliant with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection are requested.

Claim Rejection - 35 U.S.C. § 112, first paragraph, written description

Claim 5, and dependent claims 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, and 156-157 are rejected under 35 U.S.C § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner asserts that the specification does not teach fusion proteins designed by protein engineering on a template or *de novo* protein design. Applicants traverse the rejection.

The specification provides ample support for engineered proteins in which protease domains and polypeptide targeting domains have been selected and combined according to a specific design. The section entitled "F. Exemplary Methods for Designing Adzymes" (paragraphs [0418]-[0434]) discloses methods for engineering desired properties into candidate structures. Paragraph [0420] states that "[g]ood candidates...may be linked together using various types of linking strategies," such as insertion of functional parts from disparate enzymes into loops, or attachment to amino acid sequences or other structures. Other paragraphs describe how properties such as "association and dissociation properties, on-rates, off-rates, and catalytic reaction rates...are engineered into the molecules by a combination of rational, structure based design and manufacture of a multiplicity of candidate constructs, or sub-parts thereof..." (paragraph [0427]). Properties of candidate adzymes may be "further enhanced by one or more rounds of mutagenesis and additional selection/screening" (paragraph [430]). Thus, Applicants submit that the specification provides adequate description of polypeptides engineered for specific properties.

MPEP 2163 provides guidance for evaluating compliance with the written description requirement. As is true when conducting any written description analysis, the "requirement must be applied in the context of the particular invention and the state of the knowledge ... As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." MPEP 2163; *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

MPEP 2163 provides specific guidance for evaluating whether Applicants have satisfied the written description requirement for claims directed to the genus. "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics." MPEP 2163; See *Eli Lilly*, 119 F.3d 1559 at 1568. Thus, the question in this case is whether Applicants' disclosure is sufficient to show possession of the claimed genus.

Applicants submit that the present case is akin to *Capon v. Eshhar*. The specification provides ample description exemplary of the claimed genus to plainly indicate to one of skill in the art that Applicants had possession of the claimed invention.

Nevertheless, and solely to expedite prosecution, Applicants have amended claim 5 to delete reference to the term "engineered". Applicants understand that the Examiner envisions the term "engineered" to include polypeptides created completely de novo (e.g., no portion of the polypeptide corresponds to a naturally occurring polypeptide sequence), and thus have amended the claims to improve their clarity. The amendments are made solely to expedite prosecution and are not in acquiescence to any of the arguments advanced by the Examiner. Applicants expressly reserve the right to prosecute claims of similar or different scope in future applications, as well as to present additional arguments or evidence relevant to this grounds of rejection. In view of Applicants' amendment, reconsideration and withdrawal of the rejection are requested.

Claim Rejection - 35 U.S.C. § 112, first paragraph, enablement

Claim 5, and dependent claims 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, and 156-157 are rejected under 35 U.S.C § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner asserts that the specification does not reasonably provide enablement for an adzyme formed by the fusion of a catalytic domain and a binding domain engineered by any means. Applicants traverse this rejection.

The specification provides ample support for engineered proteins in which protease domains and polypeptide targeting domains have been selected and combined according to a specific design. The section entitled "F. Exemplary Methods for Designing Adzymes"

(paragraphs [0418]-[0434]) discloses methods for engineering desired properties into candidate structures. Paragraph [0420] states that "[g]ood candidates...may be linked together using various types of linking strategies," such as insertion of functional parts from disparate enzymes into loops, or attachment to amino acid sequences or other structures. Other paragraphs describe how properties such as "association and dissociation properties, on-rates, off-rates, and catalytic reaction rates...are engineered into the molecules by a combination of rational, structure based design and manufacture of a multiplicity of candidate constructs, or sub-parts thereof..." (paragraph [0427]). Properties of candidate adzymes may be "further enhanced by one or more rounds of mutagenesis and additional selection/screening" (paragraph [430]). Thus, Applicants submit that the specification provides adequate description of polypeptides engineered for specific properties.

The above portions of the specification are merely exemplary of the detailed guidance provided in the specification. In view of the detailed guidance and the high level of skill in the art of molecular biology as of the effective filing date of the instant application, one of skill in the art would be able to practice the full scope of the claimed invention without undue experimentation.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). "Time and expense are merely factors in this consideration and are not the controlling factors." *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

The foregoing cases provided important guidance for evaluating compliance with the enablement requirement. Where, as in the instant application, the level of skill in the art is very high, and the specification provides detailed guidance for the making and testing of a full range of embodiments within the scope of the claims, the patentability of the claimed invention is not undermined just because one of skill in the art would have to make and test certain embodiments of the claimed invention.

Nevertheless, and solely to expedite prosecution, Applicants have amended claim 5 to delete reference to the term "engineered". Applicants understand that the Examiner envisions the term "engineered" to include polypeptides created completely de novo (e.g., no portion of the polypeptide corresponds to a naturally occurring polypeptide sequence), and thus have amended the claims to improve their clarity. The amendments are made solely to expedite prosecution and are not in acquiescence to any of the arguments advanced by the Examiner. Applicants expressly reserve the right to prosecute claims of similar or different scope in future applications, as well as to present additional arguments or evidence relevant to this grounds of rejection. In view of Applicants' amendment, reconsideration and withdrawal of the rejection are requested.

Claim Rejection - 35 U.S.C. § 102

Claims 5, 7-9, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 127-129, 156 and 157 are rejected under 35 U.S.C. § 102(b) as anticipated by Holvoet *et al.* (JBC 1991, vol. 266, pp 19717-19724; herein "Holvoet"). Applicants traverse this rejection.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1978). Applicants contend that Holvoet fails to satisfy the criteria for anticipating the presently invention.

Claim 5, as amended, specifies that the polypeptide targeting domain of the claimed adzyme *reversibly binds with an address site on said substrate*. In other words, claim 5 is directed to adzymes where the targeting domain binds to the same substrate cleaved by the protease domain (e.g., the adzyme binds to and cleaves the same substrate). Holvoet does not

teach each and every limitation of the claimed invention, as set forth in claim 5. In contrast, Holvoet discloses a fusion protein where the targeting domain binds to one protein and the protease domain cleaves a different protein. Specifically, the plasminogen activator (uPA) protease domain cleaves the soluble plasminogen in the circulating blood, while the fibrin-specific antibody targeting domain binds to fibrin in a blood clot.

For at least the foregoing reasons, Holvoet fails to teach each and every limitation of claim 5, and thus fails to anticipate claim 5, as well as all claims depending from claim 5. Accordingly, Applicants submit that claims 5, 7-9, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 127-129, 156 and 157 are novel in view of Holvoet. Reconsideration and withdrawal of this rejection are requested.

Applicants note that claims 158-163 have been added as part of the instant response. Applicants take this opportunity to briefly point out why the newly added claims are also novel in view of Holvoet.

As discussed above, Holvoet provides a protein with a plasminogen activator (uPA) protease domain and a fibrin-specific antibody targeting domain. The fibrin-specific antibody targeting domain binds to fibrin in a blood clot (e.g., the substrate). Holvoet fails to teach or suggest proteins or targeting domains that bind to substrates other than a blot clot. For example, Holvoet fails to teach or suggest proteins or targeting domains that bind to an amyloid deposit or a substrate produced by a pathogen. Accordingly, for at least the foregoing reasons, Holvoet fails to anticipate new claims 158-163.

Claim Rejection Withdrawn - 35 U.S.C. § 102

Applicants note with appreciation that the rejection of claims 5, 7-9, 26- 27, 31, 37, 69-70, 72, 74, 78, 108, 117, 127-129, 156, and 157 under 35 U.S.C. § 102(b) as allegedly anticipated by Davis *et al.* has been withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claim 117 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable in view of Holvoet or Bhatia *et al.* (Intl. J. Cancer 2000, 85, 571-577; herein "Bhatia") in view of Davis *et al.* (WO 00/64485; herein "Davis"). Applicants traverse this rejection.

As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. Davis describes exemplary proteases, and was provided in an attempt to address particular added features of dependent claim 117. However, the features provided by Davis fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention.

Although not relevant to the instant rejection, Applicants take a moment to address the Examiner's response to Applicants' previous arguments. The Examiner states that Davis made fusion proteins by chemical conjugation, not by gene fusion techniques, but asserts that one of ordinary skill would be motivated to make the protein conjugate of Davis by gene fusion methodology, as taught by Holvoet or Bhatia Applicants respectfully disagree and maintain the arguments of record contrary to the Examiner's position. Applicants do not and have not acquiesced to the Examiner's position and expressly reserve the right to continue to advance arguments to counter the Examiner's position with respect to Davis in the event the reference is used to reject the amended claims in a future Office Action.

Claims 26, 27, 29 and 31 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Holvoet in view of Guo *et al.* (Biotech and Bioeng, 2000, 70, 456-463; herein "Guo"). Applicants traverse this rejection.

As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. Guo describes a fusion protein comprising L-asparaginase (ASNase), a $(Gly_4Ser)_3$ linker, and a protective scFv, and was provided in an attempt to address particular added features of certain dependent claims. However, the features provided by Guo fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention.

Claim 51 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Holvoet in view of Debburman *et al.* (PNAS 1997 94, 13938-13943; herein "Debburman"). Applicants traverse this rejection.

As described in detail above, Debburman fails to teach or suggest each and every limitation of the claimed invention. Debburman describes the role of molecular chaperones in converting prion proteins to an abnormal conformation, and was provided in an attempt to address particular additional features of dependent claim 51. However, the features provided by Debburman fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention.

Claims 131-134 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Holvoet in view of Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197; herein "Sanderson"). Applicants traverse this rejection.

As described in detail above, Sanderson fails to teach or suggest each and every limitation of the claimed invention. Sanderson describes noncovalent inhibitors for thrombin and factor Xa, and was provided in an attempt to address particular additional features of dependent claims 131-134. However, the features provided by Sanderson fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention.

In conclusion, Applicants contend that the claims are nonobvious in view of the cited references. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are requested.

Double Patenting

Claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119, 127-129, and 131-134 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 4-5, 30-34, and 37-41 of copending Application Nos. 10/792,498 and 10/650,591.

Applicants reiterate that, if conflicting claims are first allowed in these two co-pending U.S. Applications, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal

disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. In the meantime, and given that there has been no indication of allowable subject matter in the instant application, Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Applicants note that, in accordance with MPEP 804.I.B., the Examiner will maintain the provisional double patenting rejection until there are either no longer any conflicting claims or the double patenting rejection is the only remaining rejection in at least one of the applications.

CONCLUSION

Applicants submit that the application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P01-001**.

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Respectfully submitted,

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